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INUS Congress 2022 Review

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It was a great pleasure to see so many familiar faces in Innsbruck at the INUS annual congress. Despite the pandemic delays, everyone was enthusiastic to reconnect and discuss neuro-urology. Over 200 participants attended the meeting from over 30 countries. The program started with the workshops, which have always been a popular forum that lend themselves to small group discussions and interactive topics. On Thursday afternoon, INUS hosted the Urodynamics, Translational Research, and Sacral Anterior Root Stimulation workshops, and on Friday morning the Neurosciences, Sacral Neuromodulation, and Gladiators debate were conducted.

Professor Madersbacher, outgoing INUS President, introducing the timing bells. Courtesy of Robert Schober.

The workshop chairpersons (Marcio A. Averbeck & Stefania Musco, Célia Cruz & Francis Hughes, John Heesakkers, Jalesh Panicker & Alessandra Fanciulli, Bertil Blok & Marcio Averbeck, and Reynaldo Gomez) deserve a special thank you, as they all put together a great selection of speakers. Similarly, on Saturday the nurse workshop was attended by over 40 nurses. The session was chaired by Susanne Vahr Lauridsen, Helmut Madersbacher, Kornelia Buchner-Jirka & Kadir Önem, and focused on intermittent catheterization and female sexual dysfunction.

The plenary program was started with an address by the INUS president Professor Helmet Madersbacher, and a welcome to Innsbruck by the President of the Medical University Innsbruck University Professor Dr. Wolfgang Fleischhacker. Professor Madersbacher's timing bells were introduced. They were most successful at keeping speakers on time throughout the plenary! The first two keynote lectures covered neuro-urology from the viewpoint of a neurologist and a urologist, with Professor Madersbacher reminding us of the many lessons in the history of neuro-urology that should be remembered in practice today. The EAUN lecture on guideline development was a great introduction to a panel discussion on guidelines in neuro-urology, and what is needed in future guidelines. There definitely should be a way to collaborate across societies for future guidelines to try and avoid duplicating a lot of the monumental effort that goes into the creation of a guideline document. The afternoon ended with presentations and a case discussion on UTIs in neuro-urology. Despite the magnitude of this problem, there are still many opportunities for researchers to add to the evidence on this important topic. Finally, a great summary of the microbiome in neuro-urology was presented, which highlighted the potential for further studies to understand this novel research area. The evening ended with three poster sessions, in which many new and established researchers presented their novel research. Adding to the excitement was the prize offered by the Swiss Continence Society for the best poster of each session.

Saturday started with the keynote lecture on sensory and motor pathways in lower urinary tract dysfunction. A panel discussion followed on detrusor underactivity and detrusor sphincter dyssynergia, an ambitious set of topics which the panel did a great job of discussing in only 30 minutes. The SBU lecture on polypharmacy in neuro-urology and the EAN lecture on autonomic dysfunction in neuro-inflammatory disorders followed by the lecture on urogenital dysfunction in neurological disorders were quite thought provoking. We finished the morning with the PACS lecture on the importance of urodynamics in neuro-urology, and an open discussion with the audience.

After lunch, the discussion turned to surgical reconstruction and urinary diversion. This was followed by a nice video showing a new catheterizable channel creation technique (the Önem conduit).

The SIU lecture built on this subject with a discussion of Dr. Gomez's 30 years of experience with spinal cord injury-related reconstruction. The continued challenges with terminology standardization in neuro-urology were highlighted, and finally we heard about the progress Dr. Mehrad is making with spina bifida care in Iran. Dr. Castro-Diaz delivered a keynote lecture on intrinsic sphincter dysfunction, and this was followed by a series of ICS lectures which discussed the management of neurogenic stress incontinence and the technique of augmentation cystoplasty. The TAU lecture discussed novel agents for the treatment of the underactive detrusor. The last event of the day was the panel discussion on neural imaging, which brought together the expertise of neurologists, urologists, and imaging specialists.

The day ended with a spectacular gala dinner at the Hall of Music with a professional string quartet, amazing food, and great company. A tribute to Dr. Madersbacher's career in neuro-urology, and his time as INUS president was a very special part of the evening.

(left) Dr. Rizwan Hamid discussing the current management of neurogenic stress urinary incontinence. Courtesy of Robert Schober.

(above) D. Mair and A. Fürruther discuss intermittent catheterization in children during the INUS Nurse Workshop. Courtesy of Robert Schober.

On behalf of myself and Dr. Moreno-Palacios, I want to thank all the faculty and attendees who made this event a success.

To all the sponsors, a very special acknowledgement of your support, as without this, an in-person meeting could not happen. I think the pandemic has taught us that this is still an important format that allows us to share ideas, connect with colleagues, and develop new collaborations. I cannot imagine the countless hours the local organizing committee, led by Dr. Madersbacher and his team, dedicated to ensuring the scientific program, and evening events were a success. I look forward to seeing the scientific program for the INUS congress in Athens in 2023!

Interview with the Experts

Diabetic Bladder Dysfunction and NLRP3

Dr. J. Todd Purves & Dr. Francis "Monty" Hughes
Duke University School of Medicine, North Carolina, USA
Glenn Werneburg, MD, PhD, Editor, Neuro-Urology News

Dr. J. Todd Purves is Associate Professor of Surgery at the Duke University School of Medicine. He received his undergraduate degree from Cornell, followed by his M.D. and Ph.D. from University of Illinois. He then did his urology residency at the University of Arizona followed by his fellowship in pediatric urology at Johns Hopkins University. He is a surgeon-scientist, and is the recipient of many awards and grants including an NIH R01 on inflammasome-mediated inflammation in diabetic bladder dysfunction. He and his lab have published extensively in the areas of neuro-urology, and bladder dysfunction.

Dr. Francis "Monty" Hughes, Jr. is Assistant Professor at the Duke University School of Medicine. He received his Ph.D. from the Medical University of South Carolina, and performed postdoctoral fellowships at UNC Chapel Hill and the NIH. He then joined the University of North Carolina at Charlotte, where he rose the faculty ranks to Associate Professor. Following a stint as the director of the biology division of a start-up pharmaceutical company he joined with Dr. Purves. The pair then joined the faculty at Duke University School of Medicine, where Dr. Hughes serves as the Director of the Urinary Dysfunction Laboratory which studies the role of inflammation in bladder dysfunction.

The laboratory of Drs. Purves and Hughes has been instrumental in demonstrating the central importance of the NLRP3 inflammasome in sensing the biochemical stressors associated with bladder outlet obstruction and diabetic bladder dysfunction, and translating them into an inflammatory signal that leads to changes in voiding function, denervation and fibrosis.

They recently published the article **Diabetic bladder dysfunction progresses from an overactive to an underactive phenotype in a type-1 diabetic mouse model (Akita female mouse) and is dependent on NLRP3**. In this Issue, we discuss the paper and their collaboration. The interview is below, edited for length and clarity.

Glenn Werneburg: What are the clinical manifestations of diabetes mellitus in lower urinary tract function?

Todd Purves: There is a wide spectrum of presentation in diabetic bladder dysfunction. One of the earliest symptoms is a reduced sensation of bladder fullness. Because these individuals are lacking early sensation, they often also describe urgency, because they don't sense the need to void until their bladder is close to its capacity. This group, the "overactive bladder phenotype," often has urgency, frequency, urge incontinence, and reduced sensation. On the other hand, we also see patients with more severe disease. These patients, the "underactive bladder phenotype," present with overflow incontinence and often urinary tract infections.

In basic science investigations including our Akita mouse model and Danashgari's rat model, it has been shown that the overactive phenotype progresses to the underactive phenotype, but in humans the progression is less well-established, and somewhat controversial.

GW: What was the clinical impetus for this investigation?

TP: The impetus for me was the combination of the size of the problem, the lack of effective treatment, and its trajectory to get worse, not better, over the upcoming decades.

Diabetes is an epidemic. We were on pace for over one third of Americans to become diabetic by 2050. Though the trend has slowed to some extent, the numbers are overwhelming and it is a global problem. Diabetic bladder dysfunction may be more common than all of prostate cancer, stones, and incontinence combined. There remains no treatment for diabetic bladder dysfunction.

I am a pediatric urologist. At Duke, we are seeing more and more children with diabetes. We recently had a five-year-old diagnosed with type 2 diabetes. Though one would expect children to be too young to suffer from diabetes-related voiding dysfunction, we are seeing this as well. For example, in my clinic, I have an 11 year old girl with a 800 cc capacity bladder that doesn't empty well due to type 2 diabetes mellitus. These patients start to have severe problems two or three decades later.

GW: Your joint group previously reported on the overactive bladder phenotype in the diabetes mouse model at 15 weeks of age. Describe the results of that study, and how they provided the framework for the current investigation.

Monty Hughes: Diabetic bladder dysfunction (DBD) is not corrected by strict glucose control and this is thought to be due to the activation of bladder inflammation by previously glycated proteins and lipids (so called "metabolic memory") as well as numerous diabetic metabolites. We were intrigued as to how this occurs and we settled on the NLRP3 inflammasome as the most likely sensor that recognizes these molecules and triggers inflammation.

In the first part of this study, we showed that many of these molecules activate NLRP3 in urothelial cells, setting the stage for the in vivo work. For that work we chose the Akita diabetic type 1 genetic mouse model, which we could crossbreed with NLRP3 knockout mice to unequivocally demonstrate the importance of NLRP3.

Previously, Danashgari had proposed that DBD follows a temporal progression from overactive to underactive bladder, although, as Todd mentioned, the clinical progression in humans is less well-established. So we looked for signs of bladder dysfunction in the females of these mice, which had less hyperglycemia than the males and thus seemed likely to progress more slowly and increase our chances of finding the distinct stages (overactive bladder phenotype and underactive bladder phenotype) proposed by Daneshgari. Indeed, we found overactive bladder symptoms at 15 weeks of life and so we performed these initial studies at that time point. We found that knocking out NLRP3 completely prevented bladder inflammation while having no effect on hyperglycemia. Most importantly, it prevented the development of any symptoms of overactive bladder such as increased urinary frequency and decreased voiding volume, as measured by urodynamics.

One critical event that occurs during DBD, which is thought to make it more or less irreversible, is a loss of neurons or denervation. Since we had previously implicated NLRP3 in denervation during bladder outlet obstruction, we thought it might play an important role here. Indeed, we found that knocking out NLRP3 completely blocked the reduction of nerve density and number caused by diabetes. Carrying this further, we sought to determine if denervation was general or related to symptoms patients might experience. As Todd mentioned, DBD patients typically have a reduced sense of fullness. This sensation is thought to be carried by A-delta fibers. We found that A-delta fibers were indeed decreased and the reduction was blocked in the NLRP3 knockout animals. We also examined C-fibers which carry pain messages and are thought to mediate OAB symptoms. We actually found these neurons increased in the urothelium in response to diabetes and this increase was again blocked in the NLRP3 knock out animals. So the exciting conclusion of that work was that NLRP3 was mediating OAB symptoms and symptom-specific innervation. This, of course, made us curious if NLRP3 might be controlling the progression to underactive bladder as well.

GW: And this led to the current study. What were its main findings and implications?

MH: In this study, we found that DBD in the female Akita mice had progressed from overactive bladder at 15 weeks to underactive bladder at 30 weeks (as indicated by decreased voiding frequency and increased voiding volume), which makes it entirely consistent with Daneshgari's proposed temporal model of DBD. Moreover, crossing this mouse with various geneticall-y modified mice allowed us to define the molecular events that cause this progression. In crossing these mice with NLRP3 knockouts, we found that even at 30 weeks there was no inflammation in the bladder if NLRP3 was absent. This alone seemed remarkable as there are presumably other redundant pathways to elicit inflammation, but clearly NLRP3 is by far the major, if not only, player in bladder dysfunction during diabetes. This can vastly simplify the search for a molecular target to alleviate DBD. Most importantly, knocking out NLRP3 prevented the appearance of underactive bladder signs in cystometry. A major contribution to bladder dysfunction is hypertrophy of the smooth muscle and we also showed that this hypertrophy was blocked in the NLRP3 knockout animals.

GW: Based on the findings of the study, could targeting NLRP3 be a viable approach to the treatment of diabetic bladder dysfunction? How could such targeting be accomplished?

TP: Blood sugar control is necessary but not sufficient to prevent DBD. Metabolic dysregulation leads to hyperglycemia, but there are also other products such as HMGB1 and uric acid, that cause inflammation. Unlike the cardiothoracic effects of diabetes, where risk is significantly reduced when sugars are controlled, the bladder remains subject to DBD even when sugars are well-controlled.

NLRP3 inhibitors may play the largest role in the newly diagnosed diabetic, prior to the development of bladder dysfunction. We know that inflammation occurs and is important for DBD, but we don't yet know when it is important. We envision NLRP3 inhibitors being useful as an adjunct therapy to glucose control in patients who have not yet developed bladder dysfunction. We think that in this way, they may prevent the inflammatory component of diabetes and thus prevent the bladder from deteriorating.

As part of our current R01, we are investigating the effect of NLRP3 knockout in animals with well-controlled diabetes, poorly-controlled diabetes, and not at all controlled diabetes. It will be interesting to see if, when sugars are maintained at normal levels at all times, the animals still develop bladder dysfunction.

In urology, we generally don't see our patients until problems have already developed. By the time we see this group of patients, the inflammatory process in DBD has already started, and we may have missed the window wherein NLRP3 inhibition may have been beneficial. We are now interested in resolution pharmacology and "specialized pro-resolution mediators". These molecules act as NLRP3 inhibitors. Not only do they put the brakes on inflammation, but they also may be able to help reverse the metabolic memory that occurs during the time when inflammation is important in leading to the bladder dysfunction. We're hopeful that this approach may ultimately be able to help the patients who have had longer term diabetes and lower urinary tract symptoms.

GW: Do you think the findings of this study might be applicable to overactive bladder, even in the absence of diabetes?

TP: Yes. The most obvious one is obesity. We make the clinical distinction between diabetes and obesity, but really there is a spectrum. The same DAMPs that are generated from abdominal adipose, also activate the inflammasome, and cause the inflammation we described.

Our findings may be generalizable to any bladder condition that leads to inflammation and overactivity.

MH: We've also shown that NLRP3 is implicated in at least two other models of overactivity: cyclophosphamide-induced hemorrhagic cystitis, and bladder outlet obstruction. I group all these conditions together and call them Urinary Complications with an Inflammatory Component, or UCICs. We think that NLRP3 inhibition might be very useful in any of the UCICs including bladder outlet obstruction, cyclophosphamide-induced hemorrhagic cystitis, diabetes, and probably interstitial cystitis. NLRP3 has also been implicated in induced conditions such as stent-related inflammation. Our findings may apply to any of the benign urological disorders with a significant inflammatory component.

GW: What advice do you have for junior INUS members interested in embarking on a career as a surgeon-scientist with a neuro-urological focus?

TP: Junior INUS members have already made the first good step: getting plugged in with neuro-urologists who are surgeon-scientists, and a society that supports this. At different phases of one's training, one needs to consider the neuro-urology environment and expertise. As a medical student, one should consider residency programs with a neuro-urologist on staff. Similarly, as a resident, one should consider fellowships with a neuro-urological focus. If there are not any neuro-urologists at one's institution, pediatric urologists are a great resource. They often have spina bifida clinics, practice neuro-urology, and are often plugged in with the community. Large conferences such as EAU, AUS, and SUFU, can be overwhelming, and often there is less neuro-urological focus. Conferences such as the INUS Congress and the Society of Pelvic Research are great opportunities to make connections with those performing translational neuro-urological research, and to get exposure to the field and the newest work.

It is also advantageous to seek out a fellowship wherein there will be support and opportunities for the development of a K award, or other career-development grant, proposal. Ideally, one would have the proposal written by the end of fellowship, with the goal of submitting soon after embarking on one's next job. This will lead to early financial support for research and one's career as a surgeon-scientist.

GW: Do you think your respective clinical and basic science expertise has led to new opportunities for pioneering research? Do you think such relationships between surgeons and basic scientists will be critical to move the field forward?

TP: I strongly believe this is the way to do science if you're a clinician. I could not have done this without Monty. Running a lab full time and a surgical practice full time is not possible. There are people with Ph.D.'s running laboratories 80 hours per week, and they're not seeing patients or taking call. It just isn't possible, as a clinician, to compete with that. As a surgeon-scientist, I think pairing up with someone at a very high level is critical. This individual should be a scientist in his or her own right, and be able to run a laboratory independently. Monty and I are fortunate in that I'm also a trained scientist. So it's not like he's doing all the science and I'm just providing cover. I think it is a great model, and works very well for us. What the basic scientists get out of this, is that the work is very clinically-driven. For example, in our papers and grants, the focus is always on the clinical picture. Clinician-scientists are on the front lines, with the unique vantage point to see what is clinically needed. We need someone to panic about diabetic bladder dysfunction, for example. The Ph.D.'s aren't going to do it, because they're not seeing 12-year-olds who are already having bladder overactivity.

Monty and I are great collaborators, but would be lousy co-conspirators because we won't let each other get away with anything. For example, I may come to him with an idea, and he'll tell me that the tools to address it aren't available, or that it would cost $15 million and take ten years. Conversely, he may come to me with an idea, and while scientifically interesting, may not be clinically important. It helps to have a clinical practice guide the ship. For example, it avoids focus on problems that are not clinically important. I think that has gotten away from us in urology, because there are fewer and fewer scientifically literate and scientifically interested clinical urologists. It's rare that people are willing to design investigations and carry out the work to make big discoveries.

As someone who has a Ph.D. in biophysical chemistry, and trained as a pediatric urologist, I would not be able to do this without Monty. I would have these great ideas, but lack the bandwidth to dive deep. It is really critical to make sure the work is not just well-received by the clinicians, but also by the scientists. In this way, it also helps to have this partnership in that I can field clinical criticisms, and Monty can field those from the basic science community. In this way, our work has been accepted in both areas.

MH: Todd is the lead singer, and I'm more the manager and the drummer. The importance of the collaboration, from my perspective, is the clinical relevance. As basic scientists, we tend to run down these rabbit holes, because they're really exciting, but they may not lead to anything more than just more basic science. In the past, as an independent investigator, and associate professor with tenure, my grant proposals would often get critiqued by the NIH for lacking clinical relevance. I'd run them by every scientist in my department, but at the time I didn't have any M.D.'s who could really lend their insight. Although I did get some funding, I certainly wasn't as successful as we are now. I think NIH really appreciates the clinical focus, and the idea that the work is important.

This collaboration has turned out to be great for both of us. In fact, as part of a recent promotion, I was offered the opportunity to be independent. I felt that our collaboration has been so productive and valuable, that I opted to maintain the partnership.

TM: Neuro-urology is a small field. If anyone ever wants to talk to me about the field or career plans, or if there's anything I can do to help, please reach out. For any younger people who have the interest in it, I'm willing to do whatever I can to help. It will be great to see you all at the meetings over the next decade or so.

Meet the Board Member

Howard B. Goldman, MD
Professor of Urology, Cleveland Clinic
INUS Promotion Officer

Howard B. Goldman is Professor of Urology at Cleveland Clinic Lerner College of Medicine and an expert in quality and patient safety serving as the Institute Vice Chairman for Quality at the Glickman Urologic Institute. He has a joint appointment in the departments of Urology and Obstetrics and Gynecology and is actively involved in the training of fellows and residents, including serving as Fellowship Director for Female Pelvic Medicine and Reconstructive Surgery in the Department of Urology at the Cleveland Clinic. He has directly trained over 35 fellows and residents who are specialized FPMRS practitioners.

Dr. Goldman's clinical interests are in the medical and surgical treatment of urinary incontinence and other types of voiding dysfunction, neuromodulation, prolapse repair, complex reconstructive female urologic surgery, robotic pelvic surgery and neurourology. His contributions to the literature have been prolific, including author of over 250 articles and book chapters, editor of three textbooks and panel member for a number of standardization, guidelines and best practice statement panels. Within the AUA, he has been on the SUI Guidelines as well as Urodynamics guidelines committees. Within ICS he has been on the male LUTS terminology committee as well as the ICS/IUGA female prolapse terminology committee. He also led the group that developed the ICS sacral neuromodulation best practices document.

His prominent international reputation has led to invitations as visiting professor in the United States and abroad as well as numerous invited lectures. He is on the editorial board of a number of journals and is a former Assistant Editor of the Journal of Urology.

He is currently the co-director of the AUA annual review course for the American Board of Urology exam and co-editor of the AUA oral board review study guide, is on the ICS Education committee, the IUGA scientific committee and on the board of directors of SUFU and INUS. He was the scientific co-chair for the 2020 ICS annual meeting, was the program co-chair for the 2020 SUFU meeting, was on the program committee for the 2020 International Neuro-Urology Society and is the International Consultation on Incontinence committee chair for surgery for male incontinence.

Dr. Goldman has been involved in and led numerous projects related to innovative treatments utilizing stem cells for SUI, neuromodulation, outpatient female reconstructive robotic surgery, utilization of urodynamics, management of complications and improvements in safety and efficiency in pelvic floor surgery. Dr. Goldman is an astute physician-scientist, nurturing educator, model leader, and unwavering patient advocate renowned in the field of urology. Outside of urology, he enjoys traveling and spending time with his family including his five grandchildren.

Dr. Goldman (left) at a recent gathering with his family.

INUS Calendar

INUS Session at ICS 2022
Vienna, Austria
September 7-10, 2022

42nd Congress of the Société Internationale d'Urologie
Montreal, Canada
November 9-13, 2022

INUS Lectures at the 2nd Meeting of the Mexican Society for Urogenital Sciences
Tlaxcala, Mexico
September 28-October 1, 2022

INUS Annual Congress 2023
Athens, Greece
June 8-10, 2023